High Serum YKL-40 Level after Surgery for Colorectal Carcinoma Is Related to Short Survival

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BACKGROUND. YKL-40 is a member of family 18 glycosyl hydrolases. YKL-40 is a growth factor and may stimulate migration of endothelial cells. YKL-40 may also play a role in inflammation and degradation of connective tissue. Elevated preoperative serum YKL-40 levels in patients with colorectal carcinoma are associated with a significantly poorer prognosis compared to patients with normal serum YKL-40. In the current study the authors evaluated the value of serum YKL-40 in monitoring patients with colorectal carcinoma.

METHODS. YKL-40 was determined by an in-house radioimmunoassay method in serum obtained pre- and postoperatively from 324 patients who underwent curative resection (Dukes Stage A: 47; B: 148; C: 119; and D: 10). The patients were followed with serum YKL-40 levels every 6 months postoperatively, and the median followup time was 82 months (range, 68–95). In that period 146 patients died.

RESULTS. Serum YKL-40 was significantly decreased in the first postoperative blood sample in 62% of patients with high preoperative levels. In addition, patients with high serum YKL-40 (adjusted for age) six months after curative operation had significantly shorter survival times ($P = 0.0002$) and shorter relapse free intervals ($P = 0.004$) than patients with normal postoperative serum YKL-40. This result was independent of simultaneous serum carcinoembryonic antigen levels at six months. Analysis of survival by scoring serum YKL-40 as a time-dependent covariate in a Cox regression analysis showed that patients exhibiting elevated serum YKL-40 had an increased hazard for death within the following six months compared to those patients with normal serum YKL-40 level (hazard ratio [HR] = 9.6, 95% confidence interval [CI]: 6.0–15.5, $P < 0.0001$). Multivariate analysis including Dukes stage, age, gender, and tumor location as well as the time-dependent serum YKL-40 showed that high serum YKL-40 was an independent prognostic variable of survival (HR = 8.5, 95% CI: 5.3–13.7, $P < 0.0001$).

CONCLUSIONS. These results suggest that determination of serum YKL-40 during followup of patients operated on for colorectal carcinoma might be useful for monitoring curatively resected patients. ***Cancer* 2002;95:267–74.**

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Colorectal carcinoma is the third most frequent cancer in developed countries and is the second most common cause of death from cancer in western countries.[1,2] Approximately 40–50% of all patients undergoing curative resection for colorectal carcinoma may die of recurrent disease and metastasis.[3–5] Reports suggest that half of the recurrent cancers may be detected within the first year after surgery, and 80–90% of all recurrences may be detected within the first three years.[4] Therefore, new informative prognostic markers, which may identify high-risk patients after curative resection, are urgently needed for selection of patients for adjuvant treatment.[3] In addition, postoperative surveillance after curative resection of colorectal carcinoma may be beneficial to give patients a second option for curative surgery. Serologic markers may be an option to perform such surveillance analyses,[6] and serum carcinoembryonic antigen (CEA) has been proposed as such a marker.[7]

YKL-40 is a member of the mammalian family of 18 glycosyl hydrolases.[8–10] It is a heparin and chitin-binding lectin[10,11] without chitinase activity.[8,12] The biologic function of YKL-40 is not known in detail, but it has been shown that YKL-40 is a growth factor for connective tissue cells[13,14] and a potent migration factor for endothelial cells.[15] Furthermore, the pattern of its expression in normal and disease states suggest a function in inflammation and/or degradation and remodeling of the extracellular matrix.[16–18] YKL-40 is secreted in large amounts in vitro by the MG63 human osteosarcoma cell line[19] and is expressed selectively by murine mammary tumors initiated by *neu*/*ras* oncogenes.[9] The gene for YKL-40 has been sequenced[20] and a search of the YKL-40 protein sequence against the dbest database at the NCBI using the BLAST program has shown that several types of cancer cells, including colorectal carcinoma, express the protein.

Recently, we reported that increased levels of YKL-40 in serum are found in patients with metastatic breast carcinoma[21] and in patients with all stages of colorectal carcinoma.[22] Like CEA, YKL-40 cannot be used as a single screening test for colorectal carcinoma, since only 26% of patients with colorectal carcinoma have elevated serum YKL-40 levels at the time of operation.[22] It has been suggested that high serum YKL-40 levels might be useful as an independent preoperative predictor for poor survival in patients with colorectal carcinoma.[22] However, a prognostic marker specifically associated with the presence of a tumor may be changed by resection of the tumor. Therefore, the aim of the current study was to evaluate changes in pre- to postoperative serum YKL-40 levels in patients who underwent curative resection for colorectal carcinoma to determine whether postoperative elevation in serum YKL-40 levels may be related to relapse or short survival time.

MATERIALS AND METHODS

Serum YKL-40 levels were determined in samples from healthy volunteers and in pre- and postoperatively obtained samples from patients who underwent curative resection for colorectal carcinoma.

Healthy Volunteers

The normal range of serum YKL-40 was determined in 260 healthy volunteers,[23] including 144 females and 116 males with a median age of 48 years (range, 18-79 years). Serum YKL-40 may potentially vary with time. Therefore, the normal variation in serum YKL-40 levels was evaluated in 30 healthy women aged 24-62 years. Serum samples were collected from them five times at seven days intervals. After three years serum samples were again collected five times at seven days intervals from 21 of these women.

Patients

The study population participated in a Danish multicenter study of patients who underwent elective large bowel resection for primary colorectal carcinoma. The patients were enrolled between April 1991 and August 1993 and represented 20 Danish hospitals, described in detail elsewhere.[24] The disease was staged according to Dukes original classification with the addition of a D group that identified patients with distant metastasis.[25] Time to first relapse and survival time after the operation were registered in all patients undergoing curative resection. None of the patients received preoperative and/or postoperative adjuvant chemo- and/or radiotherapy, as these modalities were not part of the standard treatment regimen in Denmark at that time. Patients were followed in the outpatient clinic every three months for five years or until death. At each followup examination, the assessment included a medical history, a clinical examination, a full blood count, and liver enzymes. Additional investigations (e.g., digital rectal examination, endoscopy, gynecologic examination, ultrasonography, colonoscopy, chest radiography, and computed tomography scanning) were performed when appropriate. Recurrences were classified as either locoregional or distant metastases. Local recurrence was defined as tumor growth in the region of the primary radical operation, including the surgical wound, and demonstrated clinically or by imaging techniques but not necessarily verified by biopsy. Patients who developed recurrent disease were not referred to chemo- and/or radiotherapy.

Five hundred forty six patients were included in the study. In 128 of these patients the operation was

TABLE 1
The Numbers of Patients Followed with Blood Samples for the Given Number of Months after Curative Operation for Colorectal Carcinoma

	Duration of serial blood test after curative operation for colorectal carcinoma months									
Stage	6	12	18	24	30	36	42	48	54	60
Dukes A (n = 47)	1	1	1	9	12	8	9	2	3	1
Dukes B (n = 148)	17	17	9	11	14	30	23	18	6	3
Dukes C (n = 119)	19	17	12	11	16	22	13	7	2	0
Dukes D (n = 10)	4	3	0	0	1	0	1	1	0	0

only palliative. Curative resection was performed in 418 patients, and corresponding pre- and postoperative serum samples (taken at six month intervals) were available from 324 of these patients, including 192 men and 132 women with a median age of 68 years (range, 37–90). One hundred ninety seven patients had colon carcinoma and 127 had rectal carcinoma. The duration of the blood sample period in patients who underwent resection is shown in Table 1.

The study was performed in accordance with the Helsinki II declaration, and the patients were informed about the possibility of withdrawing from the study at any time. The Central Ethics Committee, the Danish Board of Health, and the Danish Data Protection Agency approved the research protocol.

Biochemical Analysis

Blood samples were taken in the morning before surgery and postoperatively at six month intervals for five years or until death. Serum was separated from cellular elements by centrifugation within one and a half hours after blood sampling. All serum samples were stored at −80 °C until analysis. Serum YKL-40 was determined by an in-house radioimmunoassay method[26] using rabbit antibody raised against human YKL-40. Purified human YKL-40 was used for a standard and tracer. The intra-assay and inter-assay variations were $< 6.5\%$ and $< 12\%$ respectively, and the sensitivity was 20 μg/L. Serum CEA was measured using the Immulite CEA assay (Euro/DPC Ltd., Llanberis, Gwynedd, UK). The threshold for elevated serum CEA was 5.0 μg/L.[7]

Statistical Analysis

The SAS® software package (version 6.12; SAS Institute, Cary, NC) was used to manage patient data and to perform statistical analyses. A normal reference region was calculated as described by Royston[27] on the log transformed serum YKL-40 values of the healthy controls adjusting for age, and the 95th percentile was chosen for the upper limit. The serum YKL-40 levels in the patients were scored as normal or elevated by the normal age adjusted serum YKL-40 level as described above. The endpoints for survival analysis were recurrence (local or metastatic) and death of all causes. The Kaplan-Meier method was used to estimate survival probabilities, and the log-rank test was used to test for equality of strata. The Cox proportional hazards model was applied for multivariate analysis, including time-dependent covariates. The assumption of proportional hazards was verified graphically where applicable. Analysis of repeated measurements was done using time dependent covariates in the Cox proportional hazards model. The serum YKL-40 measurements were scored as normal or elevated by the normal age adjusted serum YKL-40 level using three time dependent variables: one for the period 0 to 6 months from the last available YKL-40 measurement, one for the period 6 to 12 months from the last YKL-40 measurement, and one for the period exceeding 12 months from the last measurement. Rank statistics were used to calculate correlation coefficients and to test hypotheses on location. Tests of independence were done using the chi-square test. The significance level was set to 5%.

RESULTS

Serum YKL-40 in Healthy Volunteers

The median serum YKL-40 level was 102 μg/L (range, 38–514 μg/L, upper 95th percent confidence limit in all healthy volunteers = 247 μg/L), with a weak correlation to age (Spearman 0.30). There was no difference in levels of females and males ($P = 0.65$, Wilcoxon two sample test). The coefficient of variation in the log transformed serum YKL-40 values in the healthy women, who had samples collected five times at three year intervals, was 5%.

Patients Curatively Resected for Colorectal Carcinoma

The distribution by Dukes stage among the 324 patients was: Dukes A, 47 patients; Dukes B, 148 patients; Dukes C, 119 patients; and Dukes D, 10 patients. The median followup time was 82 months (range, 68-95 months), and in this period 146 patients died (Dukes

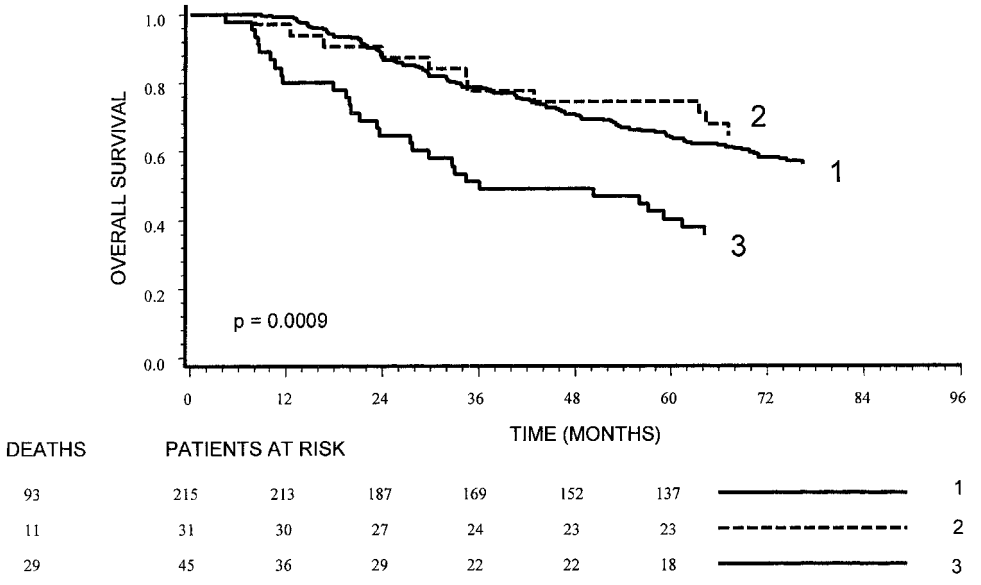

FIGURE 1. The impact of serum YKL-40 level on overall survival of 324 patients with curative resection of colorectal carcinoma. The patients were grouped by high versus normal (age adjusted) serum levels of YKL-40 obtained preoperatively and six months after the operation. The strata are: 1) patients with normal serum YKL-40 level preoperatively and at the first control six months postoperatively; 2) patients with elevated serum YKL-40 preoperatively and a normal level six months postoperatively; and 3) patients with normal or elevated preoperative serum YKL-40 and an elevated serum YKL-40 level six months postoperatively. The cutoff limit used for the determination of high versus normal serum YKL-40 was the 95th percentile of the serum YKL-40 concentration in healthy persons. Patients without YKL-40 analysis six months after the operation were excluded ($n = 33$). The P value shown is for the log rank test for equality of strata. The number of deaths is shown for stratum 1, 2, and 3, respectively, and the number of patients at risk in each stratum is shown for 0, 12, 24, 36, 48, and 60 months, respectively.

A, 9 patients; B, 54 patients; C, 75 patients; and D, 8 patients).

Serum YKL-40 Levels in Patients

The median preoperative level of serum YKL-40 was 160 μg/L (range, 56–1216), and the preoperative serum YKL-40 level was elevated above the age-corrected 95th percentile of healthy volunteers in 19% of the patients. After curative resection serum YKL-40 was significantly decreased in the first postoperative blood sample (taken six months after the operation) in 62% (34 out of 55) of these patients with elevated preoperative serum YKL-40, and in 31 patients in particular the level decreased to a level within the normal range. In addition, among the patients with normal preoperative levels, 19% had a significant decrease in serum YKL-40 six months after the operation. By Dukes classification 33% of the Stage B patients and 24% of the Stage C patients had a significant decrease at six months. Of the 236 patients with normal preoperative YKL-40 levels, 9% had elevated levels at six months.

Serum CEA Levels

Corresponding pre- and postoperative determinations of CEA were available from 286 patients. The median preoperative level of CEA was 3.10 μg/L (range, 0.25–820), and the median postoperative level at six months was 2.10 μg/L (range, 0.20–3391). We were unable to show an association between preoperative serum CEA and YKL-40 ($P = 0.68$). Fifty five patients had elevated serum CEA at six months, and only 17 of these had simultaneously elevated serum YKL-40.

Serum YKL-40 Levels in Relation to Survival

The preoperative serum YKL-40 level predicted shorter survival for the patients undergoing curative resection with elevated serum YKL-40 in a proportional hazards model including Dukes stage, tumor location, age, and gender (hazard ratio [HR] = 1.4, 95% confidence interval [CI]: 1.0–1.9, $P = 0.04$). The YKL-40 level in the first blood sample available after the operation (i.e., taken after six months) predicted shorter survival of curatively operated patients with elevated serum YKL-40 compared with patients with a normal serum YKL-40 (HR = 2.1, 95% CI: 1.4–3.2, $P = 0.0002$). The Kaplan-Meier plot is shown in Figure 1. Of the patients with elevated serum YKL-40 level six months after the operation, 36% died within 24 months, compared to only 12% of the patients with normal serum YKL-40. There was no difference in survival between patients with normal serum YKL-40

TABLE 2
Independent Prognostic Variables of Survival and Recurrence Free Interval from the Cox Multivariate Analysis

	Survival			Recurrence free interval		
Covariate	*P* value	HR	95% CI	*P* value	HR	95% CI
YKL-40 (high vs normal)						
0–6 months[a]	< 0.0001	8.5	5.3–13.7	< 0.0001	6.9	3.5–13.4
6–12 months[a]	0.004	3.4	1.5–7.9	0.20	2.5	0.6–10.6
>12 months[a]	0.13	1.7	0.9–3.2	0.40	1.7	0.5–5.8
Stage						
Dukes B vs A	0.01	2.5	1.2–5.1	0.12	2.0	0.8–4.5
Dukes C + D vs. A	< 0.0001	6.1	3.1–12.4	< 0.0001	6.4	2.9–14.0
Age (years)	0.004	1.03	1.01–1.04	0.65	1.00	0.99–1.02
Gender (female vs male)	0.11	0.8	0.5–1.1	0.40	0.8	0.6–1.3
Localization (rectum vs. colon)	0.0007	1.8	1.3–2.5	< 0.0001	2.2	1.5–3.2

HR: relative hazard ratio; CI: confidence interval.
[a] After last YKL-40 measurement. YKL–40 was updated for every six month follow-up.

preoperatively and six months after the operation, and the patients with high preoperative serum YKL-40 but with a normal serum YKL-40 six months after the operation. In a multivariable analysis including postoperative serum YKL-40 level at six months, Dukes stage of disease, age, gender, and tumor location, it was shown that patients with elevated serum YKL-40 level had a significantly poorer prognosis than those with normal level (HR = 1.8, 95% CI: 1.2–2.8, $P = 0.004$).

A similar analysis of the 286 curatively operated patients with available serum CEA levels showed that elevated CEA ($n = 55$) at six months predicted a shorter survival (HR = 4.0, 95% CI: 2.7–6.0, $P < 0.0001$). Inclusion of both serum CEA levels and serum YKL-40 levels showed that elevated levels of CEA and YKL-40 independently predicted shorter survival (serum CEA: HR = 3.7, 95% CI: 2.5–5.6, $P < 0.0001$; serum YKL-40: HR = 1.7, 95% CI: 1.1–2.7, $P = 0.03$).

One hundred forty six of the curatively operated patients died during followup, and 27% of these patients had elevated serum YKL-40 at last examination. The median time to death from the last available blood sample was 10 months (quartiles 4 and 23 months). Fifty two patients died within six months after the last available blood sample, and 22 of these patients had elevated serum YKL-40 at last examination. Seventy two percent ($n = 28$) of the patients with elevated serum YKL-40 and 52% ($n = 56$) of the patients with normal serum YKL-40 level at the last examination died within the following year. One hundred seventy eight curatively operated patients did not die during the study period, and the median time from operation to collection of the last blood sample was 37 months (quartiles 30 and 43 months). Eighty three percent ($n = 148$) of these patients had normal and 17% ($n = 30$) had elevated serum YKL-40 level at last examination.

Sixty percent (n = 193) of the patients had normal serum YKL-40 at all examinations and 10% (n = 32) had elevated serum YKL-40 at all examinations. Of the patients with normal preoperative level of serum YKL-40, 26% (n = 68) progressed to elevated serum YKL-40 during the followup. The analysis of serum YKL-40 in a Cox regression analysis including the level as a time dependent covariate (updated at each six month examination) showed that curatively operated patients whose last postoperative YKL-40 level was elevated had an increased hazard (HR = 9.6, 95% CI: 6.0–15.5, $P < 0.0001$) for death within the next six months. This was attenuated for the time period of 6 to 12 months (HR = 3.6, 95% CI: 1.6–8.3, $P = 0.003$) and not significant for the time period 12 months after the last available YKL-40 measurement ($P = 0.09$). Analysis of survival scoring serum YKL-40 as a time-dependent covariate in a multivariate Cox regression analysis including Dukes stage, age, gender, and tumor location showed that curatively operated patients exhibiting elevated serum YKL-40 had a higher hazard (HR = 8.5, 95% CI: 5.3–13.7, $P < 0.0001$) for death within the first six months after the YKL-40 measurement than patients with a normal postoperative serum YKL-40. The hazard ratio was reduced for the time period 6 to 12 months (HR = 3.4, 95% CI: 1.5–7.9, $P = 0.004$), and after 12 months there was no significant difference in the hazards ($P = 0.13$) (Table 2).

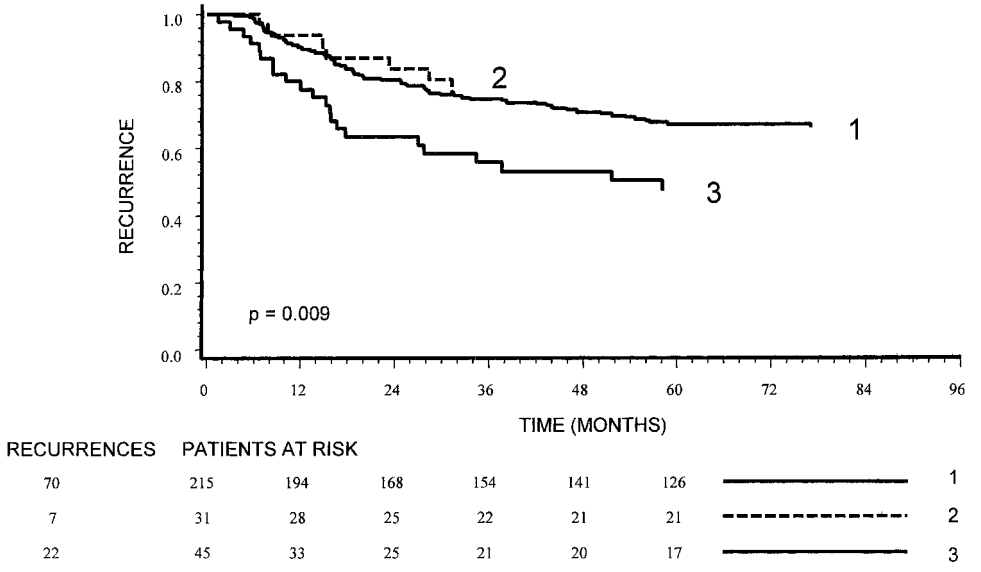

FIGURE 2. The impact of serum YKL-40 level on relapse free intervals in 324 patients with curatively resected colorectal carcinoma. Patients were divided into three groups according to high versus normal (age adjusted) serum level of YKL-40 obtained preoperatively and six months after the operation. The strata are: 1) patients with normal serum YKL-40 level preoperatively and at the first control six months postoperatively; 2) patients with elevated serum YKL-40 preoperatively and a normal level six months postoperatively; and 3) patients with normal or elevated preoperative serum YKL-40 and an elevated serum YKL-40 level six months after the operation. The cutoff limit used for the determination of high versus normal serum YKL-40 was the 95th percentile of the serum YKL-40 concentration in healthy persons. Patients without YKL-40 analysis six months after the operation were excluded ($n = 33$). The P value shown is for the log rank test for equality of strata. The number of recurrences is shown for stratum 1, 2, and 3, respectively, and the number of patients at risk in each stratum is shown for 0, 12, 24, 36, 48, and 60 months, respectively.

Serum YKL-40 in Relation to Recurrence

Of the 324 curatively operated patients, 33% (n = 108) developed recurrent disease during the followup: 15% ($n = 7$) of the patients with Dukes A, 21% (n = 31) with Dukes B, 53% ($n = 63$) with Dukes C, and 70% (n = 7) of the patients with Dukes D tumors. The majority (75%) of all recurrences were detected within 30 months of primary surgery. Of these patients with recurrence, 47% ($n = 51$) had local recurrence, 18% ($n = 19$) had local recurrence in conjunction with metastatic disease, and 35% ($n = 38$) developed disseminated disease without evidence of local recurrence. Of the 57 patients with metastasis, 67% ($n = 38$) had liver metastases, 23% ($n = 13$) had lung metastases, 2% ($n = 1$) had brain metastases, 2% ($n = 1$) had bone metastases, 4% ($n = 2$) had metastases to other organs, and the location of metastases was unknown in 2 patients. The median time from the last blood sample available for YKL-40 determination to recurrence detection was 3 months (range, 0–46 months). The median preoperative serum YKL-40 in the patients who subsequently developed liver metastases or lung metastases was 197 μg/L (range, 60-800 μg/L, n = 38) and 180 μg/L (range, 80-372 μg/L, $n = 13$), respectively.

By differentiation of patients with high versus normal postoperative serum YKL-40 concentration six months after the operation, the group with high postoperative serum YKL-40 had significantly shorter relapse free intervals than patients with normal postoperative serum YKL-40 (HR = 3.7, 95% CI: 2.1–6.5, $P = 0.004$, Fig. 2). Thirty six percent of the patients with elevated serum YKL-40 6 months after the operation had a relapse within the following 24 months, compared to 19% of the patients with a normal serum YKL-40. Analysis of relapse free interval scoring serum YKL-40 as a time-dependent covariate in a multivariate Cox regression analysis including Dukes stage of disease, age, gender, and tumor location showed that patients exhibiting elevated postoperative serum YKL-40 had a higher hazard (HR = 6.9, 95% CI: 3.5–13.4, $P < 0.0001$) for recurrence within the following six months than patients with a normal postoperative serum YKL-40 (Table 2).

DISCUSSION

It was recently suggested that the YKL-40 level in preoperative serum was an independent prognostic marker in patients with primary colorectal carcinoma.[22] We expected that elevated serum YKL-40 levels would return to levels within the normal range after curative resection of colorectal carcinoma, since the protein might

reflect the tumor burden. The current results showed that serum YKL-40 decreased in the first postoperative blood sample six months after the operation compared to the preoperative level in 62% of the patients who had elevated preoperative serum YKL-40. The current results also showed that curatively operated patients with elevated serum YKL-40 level six months after the resection had significantly shorter survival times and recurrence free intervals than did patients with normal postoperative serum YKL-40 concentrations. Thirty six percent of the curatively operated patients with elevated serum YKL-40 level 6 months after the operation died within the following 24 months, compared to 12% of the patients with normal serum YKL-40. Similarly, 36% of the curatively resected patients with elevated serum YKL-40 level 6 months after the operation had a relapse within the following 24 months, compared to 19% of the patients with a normal serum YKL-40. These observations suggest that postoperative measurement of the YKL-40 level in serum may identify a subgroup of patients with colorectal carcinoma that would benefit most from adjuvant therapy, since elevated YKL-40 after the operation independently may identify patients with incomplete surgical resection or micrometastatic disease. As expected, elevated serum CEA at six months postoperatively was also a predictor of short survival. Multivariate analyses showed that serum CEA and serum YKL-40 levels at six months postoperative were independent predictors of survival.

In the current study recurrence of colorectal carcinoma was detected in thirty three percent of the patients during the followup. To evaluate the benefit of serial determinations of serum YKL-40 levels in monitoring patients who had been curatively operated on for colorectal carcinoma, we included serum YKL-40 levels (obtained at six month intervals during the followup) in a time dependent multivariate analysis. The results indicate that an elevated serum YKL-40 level at a specific time-point increased the risk of recurrence within the following six months by 6.9 fold, and the risk of death within the following six months by 8.5 fold.

Although serum levels of YKL-40 may be prognostic in patients with colorectal carcinoma, it is not known in detail whether it reflects disease status and/or tumor burden. YKL-40 may be expressed and synthesized by various types of adenocarcinomas, including colorectal carcinoma (J.S. Johansen and P.A. Price, personal observations). Current immunohistochemic analyses of biopsies of colorectal carcinoma show that positive YKL-40 staining is found in some but not all cancer cells (J.S. Johansen, personal observation). Therefore, YKL-40 positive cancer cells may have a different phenotype than the YKL-40 negative cancers, and YKL-40 may reflect differences in the biology of various cancer cells within the same tumor.[28] Furthermore, YKL-40 is expressed by CD14+/CD16+ monocytes/macrophages,[29] a phenotype that is increased in patients with solid tumors, including colon carcinoma.[30] YKL-40 has growth factor activity for specific cell types involved in tissue remodeling processes[13,14] and is a potent migration factor for endothelial cells,[15] indicating a role in angiogenesis. The functional elucidation of YKL-40 in cancer might be an important objective for future studies.

Colorectal carcinoma is a neoplasm which within the tumor mass appears to include various cell clones that have diverse growth rates and metastatic potentials.[31] This may be one reason that cancer growth behavior is different among patients classified as having the same histologic/clinical stage.[28] During growth the expanding cancer cells may not only degrade the pre-existing extracellular matrix, but may also stimulate angiogenesis, inflammation, and new matrix formation by activation of stroma cells. Most therapeutic decisions regarding adjuvant therapy are determined on the basis of traditional prognostic factors, whereas new biologic factors may improve conventional approaches. It is most likely that a combination of different serologic and clinical parameters that reflect different aspects of tumor growth and metastasis will prove to identify the subgroup of colorectal patients that, independent of disease stage, have high risk of recurrent disease and a poor prognosis. Such high risk patients may be selected for frequent clinical and biochemical observation and monitoring to verify recurrent disease at an early stage. In addition, biologic markers may also be of benefit to identify patients who, independent of disease stage, may benefit from adjuvant therapy.

In conclusion, we have shown that elevated postoperative serum YKL-40 levels in patients undergoing curative resection for colorectal carcinoma was associated with a high risk of tumor recurrence and poor survival. However, YKL-40 cannot be used alone as a serologic marker for monitoring patients with colorectal carcinoma, and future studies should evaluate a set of combined tumor markers obtained after curative resection. By including serum, plasma, and tissue markers with known influence on tumor growth or inhibition it may be possible to identify patients with a high risk of recurrence and poor survival. Such patients should be offered adjuvant therapy and frequent examination in outpatient care, while patients with a low risk of recurrence would be spared an often useless adjuvant therapy. Evaluation of well characterized markers of recurrence and poor prognosis in

combination with clinical parameters are therefore urgently needed.[32]

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